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09/988,013	11/16/2001	Shui-on Leung	18733/1082	7681

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 09/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/988,013	LEUNG ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 21 July 2006 has been entered.

2. Claims 1-27 are cancelled.

Claim 28 has been amended.

3. Claims 28-32 are pending and under examination.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. This Office Action contains New Grounds of Rejections.

Rejections Withdrawn

6. The objection to the abstract as not commencing on a separate sheet is withdrawn in view of the amended abstract filed 7/21/2006.

7. The rejection of claims 28-32 under 35 U.S.C. 112, second paragraph, as being indefinite because the preamble of claim 28 recites a method of designing amino acid sequences of variable domains of a humanized antibody, whereas step (a) only determines the residue identities between amino acid sequences of a variable domain

of a monoclonal antibody and corresponding variable domains of two or more human monoclonal antibodies is withdrawn in view of the amendments to the claims.

Response to Arguments

8. The rejection of claims 28-32 and applied to newly added claims 33-37 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for introducing new matter into the claims is maintained.

Applicants' arguments have been fully considered but are not found persuasive for the following reasons. Applicant reiterates that support for the presently claimed antibody humanization method and the selection of human framework regions from two or more human antibodies, at least one human antibody for the framework regions of the light chains and at least one human antibody for the framework regions of the heavy chains and wherein the human antibody for the framework regions of the light chains is different from the human antibody for the framework regions of the heavy chains is found in at least Example 1 and Figure 1, where the framework regions of the variable domains of the heavy chain are selected from two different human antibodies, namely EU and NEWM and wherein the framework regions of the light chain is from REI. Again, applicants' reliance on Example 1 and Figure 1 in which the human EU heavy chain framework regions and the human REI light chain framework regions are selected does not provide adequate written support for the broader limitation of the present claims, which encompasses the selection of heavy chain framework regions from at least one human antibody and the selection of light chain framework regions from at

least one human antibody, which broadly embraces selecting heavy chain framework regions from four different human antibodies and selecting light chain framework regions from four different human antibodies. The selection of all four framework regions of the light chain (i.e., FR1, FR2, FR3 and FR4) from a single human antibody, REI, does not provide sufficient written support for the broader features and limitations of the present claims, inclusive to selecting each of FR1, FR2, FR3 and FR4 from different human antibodies. Further, while the as filed specification discloses the human EU framework regions were used for the humanized antibody with the exception that human NEWM was selected for FR4, this does not provide adequate written description for the selection of three or all four heavy chain framework regions (i.e., FR1, FR2, FR3 and FR4) from different human antibodies. Further, the disclosure that the selection of the human NEWM for FR4 of the heavy chain was due to lack of X-ray coordinate data for the EU sequence does not provide sufficient direction and guidance to the currently claimed limitations, i.e., the selection of three or all four heavy chain framework regions (i.e., FR1, FR2, FR3 and FR4) from different human antibodies. Applicants' reliance on the use of the REI human frameworks for the humanized light chain variable region and the use of the human EU FR1-3 regions and the human NEWM FR4 for the humanized heavy chain variable region for adequate written support for the limitations of "at least three of said framework regions are from different human antibodies" and "wherein said heavy chain framework regions are from the heavy chain regions of at least two different human antibodies", does not provide adequate written support for using the FR1, FR2, FR3 and FR4 from four different human antibodies for each of the light and

heavy chain variable domains. For example, there is no disclosure of a method for producing humanized variable domain sequences and humanized antibodies comprising said variable domain sequences wherein the heavy chain variable domain comprises a human EU FR1, a human Gal FR2, a human Jon FR3 and a human NEW FR4 as embraced by the currently claimed limitations of "at least one human antibody for the framework regions of the light chains and at least one human antibody for the framework regions of the heavy chains", "at least three of said framework regions are from different human antibodies" and "wherein said heavy chain framework regions are from the heavy chain regions of at least two different human antibodies". Applicant is invited to point out in the as filed disclosure where it is contemplated that each of the heavy chain framework regions (i.e., each of FR1, FR2, FR3 and FR4) are to be selected from different human antibodies and where it is disclosed that the light chain framework regions are to be selected from two, three, and four different human antibodies. For these reasons, this rejection has been applied to newly added claims 33-37.

Applicant relies on Example 1 and Figure 1 as clearly disclosing the residue identity for the light chain of 69.5% for FR1, 80% for FR2, 71.9% for FR3 and 72.7 for FR4. The residue identity for the heavy chain is 76.7% for FR1, 71.4% for FR2, 62.5% for FR3 and 90.7% for FR4. Applicant asserts that Figure 1 clearly provides written support for the sequence identities of "at least 62.5%" for the framework regions of the heavy chain and "at least 69%" for the framework regions of the light chain. This has been fully considered but is not found persuasive. The specification as filed does not

provide sufficient written description for the above mentioned claim limitations. Applicants' reliance on a generic disclosure and possibly a single disclosed species within the presently claimed heavy chain subgenus of "at least 62.5%" and the light chain subgenus "at least 69%" does not provide adequate written support for the broader range of framework regions that are "at least 62.5%" and "at least 69%", which encompasses framework regions having percent identities that are not disclosed and not clearly contemplated in the as-filed disclosure. Applicant was not entitled to the benefit of a parent filing date when the claim was directed to a subgenus (a specified range of molecular weight ratios) where the parent application contained a generic disclosure and a specific example that fell within the recited range because the court held that subgenus range was not described in the parent application. *In re Lukach*, 442 F.2d 967, 169 USPQ 795 (CCPA 1971). The as field specification does not describe the range of "at least 62.5%" for the framework regions of the heavy chain and "at least 69%" for the framework regions of the light chain regions. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See *In re Smith* 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05. One of skill in the art would not recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the subgenus of the claimed method in view of the single disclosed species.

For these reasons the rejection of claims 28-37 under 35 U.S.C 112, first paragraph as introducing new matter is maintained.

New Grounds of Objections/Rejections

9. Claim 31 is objected to in the recitation "any atoms within a complementarity determining regions...", which is grammatically incorrect. Consider revising with "any atoms within a complementarity determining region...".

10. Claim 28, step (e) is objected to in the recitation "variable domains of the light and heavy chain regions". Consider revising with "variable domains of the light and heavy chains" for readability of the claim.

11. Claim 33, step (a) is objected to in the recitation "amino acid sequences of variable domains". Consider revising the claim to recite "amino acid sequences of the variable domains".

12. Claims 28-32, 34 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 28-32 are indefinite in the recitation "the human antibody" in claim 28 (lines 4-5 of step (b)) because the claim recites "two or more human antibodies", making it unclear which human antibody is being referenced. See MPEP 2173.05(e).

b. Claim 32, step (h) is indefinite in the recitation "introducing the vector" because step (g) recites "at least one vector", encompassing multiple vectors and it is unclear which vector is being referenced. Consider amending step (h) to recite "introducing the vector(s)", provided no new matter is introduced.

c. Claims 28-32 are indefinite in the recitation "to design a humanized variable domain" in claim 28, step (c). As dependent upon step (b) of the claimed method, step (c) incorporates the selected framework regions with complementarity determining regions of the monoclonal antibody in the design of a humanized variable domain, however, step (b) recites the selection of human framework regions for both the heavy and light chain variable domains. Thus, are both heavy and light chain variable domains humanized, and which "humanized variable domain" is being referred to in step (c), the heavy or the light? As written, the metes and bounds of the claimed method cannot be determined.

d. Claim 32 and 37 are indefinite in the recitation "A method of producing a humanized monoclonal antibody designed according to the method of claim...", however, base claims 28 and 33 are drawn to methods of designing the amino acid sequences of the variable domains of a humanized antibody and not a method of designing a humanized monoclonal antibody as required in dependent claims 32 and 37. Thus, one of skill in the art would not be reasonably apprised of the metes and bounds of the claimed method.

e. Claims 28-32 are indefinite in the recitation "and framework regions of the heavy chain have a sequence identity of at least 62.5% and framework regions of the light chain have a sequence identity of at least 69%..." in claim 28 step (b). Are the human framework regions from two or more human antibodies selected based on being at least 62.5% and at least 69% identical to the corresponding framework regions of the monoclonal antibody to be humanized or do the framework regions merely have at least

62.5% and at least 69% sequence identity with the corresponding framework regions of the monoclonal antibody to be humanized, or are each of the human framework regions (i.e., FR1, FR2, FR3 or FR4) compared individually to the corresponding framework regions of the monoclonal antibody to be humanized and selected based on having at least 62.5% or 69% sequence identity or are the human variable regions (VH and VL) aligned and selected based on being at least 62.5% identical, particularly in view that step (a) recites "determining residue identities between the amino acid sequences of the light and heavy chain variable domains", or do all of the frameworks regions (i.e., FR1, FR2, FR3 and FR4) have to have at least 62.5% and 69% sequence identity with the framework regions of the antibody to be humanized?

f. Claims 29 and 34 recite the limitation "said framework regions". There is insufficient antecedent basis for this limitation in the claims. Base claims 28 and 33 from which claims 29 and 34 depend, respectively, recite light and heavy chain framework regions, making it unclear which framework regions are being referenced. See MPEP 2173.05(e). Further, it is unclear if the three framework regions from the different human antibodies are from the same antibody chain (i.e., heavy chain) or from both chains (i.e., heavy and light chains).

13. Claims 28, 32-33 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Singer et al (The Journal of Immunology, 150(7):2844-2857, April 1, 1993).

The claims are being interpreted as drawn to a method of designing the amino acid sequences of the variable domains of a humanized monoclonal antibody comprising determining residue identities between the amino acid sequences of the light and heavy chain variable domains of a monoclonal antibody to be humanized and the corresponding light and heavy chain variable domains of two or more human antibodies, selecting from said corresponding variable domain of two or more human antibodies at least one human antibody for the light chain framework regions and at least one human antibody for the heavy chain framework regions, wherein the human antibody for the framework regions of the light chain is different from the human antibody for the framework regions of the heavy chain and the framework regions of the heavy chain optionally have a sequence identity of at least 62.5% and framework regions of the light chain optionally have a sequence identity of at least 69% to the corresponding framework regions in the monoclonal antibody, incorporating the selected human framework regions with CDRs of the monoclonal antibody to be humanized to design a humanized light chain variable domain and a humanized heavy chain variable domain, retaining selected amino acid residues from the framework regions of the monoclonal antibody to be humanized in the corresponding framework regions of the humanized variable domain if one or more of said selected amino acids are predicted to have contacts with said CDRs and obtaining the amino acid sequences of the variable domains of the light and heavy chains of the resultant humanized monoclonal antibody. Further, the claims recite a method of producing the humanized antibody comprising the designed heavy and light chain variable domain sequences comprising the additional

steps of preparing a DNA sequence encoding the variable domains of the resultant humanized monoclonal antibody based upon the designed amino acid sequence, operable linking the DNA sequences into at least one vector comprising the constant domains of the light and heavy chain regions, introducing the at least one vector into a cell and culturing the cell under conditions to produce the humanized monoclonal antibody.

Singer et al teach a method of designing the amino acid sequences of the variable domains of a humanized monoclonal antibody 1B4 comprising determining the residue identities between the amino acid sequences of the variable domains of monoclonal antibody 1B4 and the corresponding variable domains of two or more human antibodies found in a database of human Ig sequences, selecting at least one human antibody for the framework regions of the light chain (i.e., Len) and at least one human antibody for the framework regions of the heavy chain (i.e., Gal), which have 82% and 84% sequence identity with the corresponding light and heavy chain framework regions of monoclonal antibody 1B4 and incorporating the selected human framework regions with the CDRs of monoclonal antibody 1B4 and retaining certain 1B4 framework residues in the humanized antibody deemed to be important for maintaining the affinity and specificity of the monoclonal antibody, obtaining the amino acid sequences of the variable domains of the light and heavy chain regions of the humanized monoclonal antibody 1B4 (see entire document, particularly abstract, pp. 2845-2846, 2848-2849, 2854-2855 and Fig. 1 and Table 1). Singer et al also teach a method for producing the humanized antibody comprising preparing the DNA encoding

the humanized 1B4 antibody, operably incorporating the DNA sequences into at least one vector comprising the constant domains of the heavy and light chain regions ($\gamma 4/\kappa$ recombinant antibodies), introducing the vector(s) into CV1P cells and culturing the cells under conditions to produce the humanized 1B4 antibodies (see entire document, particularly abstract, pp. 2845-2846, 2848-2849, 2854-2855 and Fig. 1 and Table 1).

Thus, Singer et al anticipate the claims.

14. Claims 28-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Leung et al [a] (US Patent 5,789,554, issued 8/4/1998, IDS reference A2 filed 4/30/2002).

The claims are being interpreted as drawn to a method of designing the amino acid sequences of the variable domains of a humanized monoclonal antibody comprising determining residue identities between the amino acid sequences of the light and heavy chain variable domains of a monoclonal antibody to be humanized and the corresponding light and heavy chain variable domains of two or more human antibodies, selecting from said corresponding variable domains of two or more human antibodies at least one human antibody for the light chain framework regions and at least one human antibody for the heavy chain framework regions, wherein the human antibody for the framework regions of the light chain is different from the human antibody for the framework regions of the heavy chain and the framework regions of the heavy chain optionally has a sequence identity of at least 62.5% and framework regions of the light chain optionally has a sequence identity of at least 69% to the corresponding framework regions in the monoclonal antibody, incorporating the selected human framework

regions with CDRs of the monoclonal antibody to be humanized to design a humanized light chain variable domain and a humanized heavy chain variable domain, retaining selected amino acid residues from the framework regions of the monoclonal antibody to be humanized in the corresponding framework regions of the humanized variable domain if one or more of said selected amino acids are predicted to have contacts with said CDRs and obtaining the amino acid sequences of the variable domains of the light and heavy chains of the resultant humanized monoclonal antibody and wherein at least three of said framework regions are from different human antibodies and wherein the heavy chain framework regions are from the heavy chain regions of at least two different human antibodies and wherein the selected amino acid residues in step (d) are within a 4.5 Angstrom radius of any atoms within a CDR of the light or heavy chain of the humanized antibody. Further, the claims recite a method of producing the humanized antibody comprising the designed heavy and light chain variable domain sequences comprising the additional steps of preparing a DNA sequence encoding the variable domains of the resultant humanized monoclonal antibody based upon the designed amino acid sequence, operable linking the DNA sequences into at least one vector comprising the constant domains of the light and heavy chain regions, introducing the at least one vector into a cell and culturing the cell under conditions to produce the humanized monoclonal antibody.

Leung et al [a] teach a method of designing the amino acid sequences of the variable domains of a humanized monoclonal antibody comprising comparing the murine variable domain framework sequences of monoclonal antibody LL2 to that of

human antibodies in the Kabat database and selecting the human REI (VL) and human EU (VH) frameworks as the frameworks onto which the LL2 CDRs were grafted, however, the FR4 sequence of human NEWM was used in place of the human EU FR4 in the heavy chain (i.e., framework regions form at least three different human antibodies (REI, EU and NEWM) and the heavy chain framework regions are from at least two different human antibodies (EU and NEWM)) and the framework regions of the EU human heavy chain and FR4 of NEWM have at least 62.5% sequence identity with the corresponding framework regions of monoclonal antibody LL2 and the framework regions of the REI human light chain have at least 69% sequence identity with the corresponding framework regions of monoclonal antibody LL2 and murine framework residues having potential CDR contacts were retained in the design of the humanized framework sequences and framework residues within 4.5 Angstrom radius of any atoms within any CDR can be retained in the humanized LL2 monoclonal antibody (see entire document, particularly example 1 at col. 11, col. 6, lines 5-9, and Fig. 1). Leung et al [a] also teaches a method of producing the humanized LL2 monoclonal antibody comprising said designed amino acid variable domain sequences comprising preparing a DNA sequence encoding the designed amino acid variable domain sequences and operably incorporating the DNA sequences into vectors comprising the human kappa and IgG1 constant regions, introducing the vectors into Sp2/0-Ag14 cells by electroporation and culturing the cells under conditions to produce the humanized LL2 monoclonal antibody (see col. 12-16 and Figs 3 and 6).

Thus, Leung et al [a] anticipate the claims.

14. Claims 28-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Leung et al [b] (Molecular immunology, 32(17-18):1413-1427, 1995, cited on PTO-892 mailed 2/20/2004).

The claims and their interpretation have been described supra.

Leung et al [b] teach a method of designing the amino acid sequences of the variable domains of a humanized monoclonal antibody comprising comparing the murine variable domain framework sequences of monoclonal antibody LL2 to that of human antibodies in the Kabat database and selecting the human REI (VL) and human EU (VH) frameworks as the frameworks onto which the LL2 CDRs were grafted, however, the FR4 sequence of human NEWM was used in place of the human EU FR4 in the heavy chain (i.e., framework regions form at least three different human antibodies (REI, EU and NEWM) and the heavy chain framework regions are from at least two different human antibodies (EU and NEWM)) and the framework regions of the EU human heavy chain and FR4 of NEWM have at least 62.5% sequence identity with the corresponding framework regions of monoclonal antibody LL2 and the framework regions of the REI human light chain have at least 69% sequence identity with the corresponding framework regions of monoclonal antibody LL2 and murine framework residues having potential CDR contacts were retained in the design of the humanized framework sequences and framework residues within 4.5 Angstrom radius of any atoms within any CDR can be retained in the humanized LL2 monoclonal antibody (see entire document, particularly the abstract, pp. 1414-1416 and Fig. 1). Leung et al [b] also teaches a method of producing the humanized LL2 monoclonal antibody comprising

said designed amino acid variable domain sequences comprising preparing a DNA sequence encoding the designed amino acid variable domain sequences and operably incorporating the DNA sequences into vectors comprising the human kappa and IgG1 constant regions, introducing the vectors into Sp2/0-Ag14 cells by electroporation and culturing the cells under conditions to produce the humanized LL2 monoclonal antibody (see entire document, particularly pp. 1414-1418 and Figs. 3-4).

Thus, Leung et al [b] anticipate the claims.

Conclusions

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827